



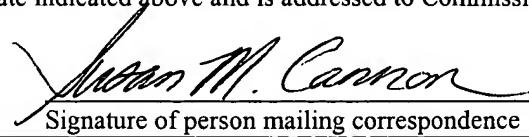
PATENT  
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Robyn Sackeyfio et al.	Art Unit:	Not yet assigned
Serial No.:	10/716,823	Examiner:	Not yet assigned
Filed:	November 19, 2003	Customer No.:	21559
Title:	COMBINATIONS FOR THE TREATMENT OF INFLAMMATORY DISORDERS		

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

### INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the enclosed Form PTO-1449.

Submission of this statement is not a representation that a search has been made, nor is the inclusion of information in this statement an admission that the information is material to patentability.

Under 35 U.S.C. § 120, this application relies on the earlier filing date of application serial number 10/191,149, which was filed on July 9, 2002.

The following references were submitted to and/or cited by the Office in the prior application and, therefore, copies of these references are not provided in this statement:

U.S. Patent 4,034,087

U.S. Patent 4,107,306

Ash et al., "The Effects of Dothiepin on Subjects with Rheumatoid Arthritis and Depression," *Rheumatology* 38:959-967 (1999)

Barden, "Regulation of Corticosteroid Receptor Gene Expression in Depression and Antidepressant Action," *Journal of Psychiatry and Neuroscience* 24:25-39 (1999)

Berberian et al., "The Addition of Topical Doxepin to Corticosteroid Therapy: An Improved Treatment Regimen for Atopic Dermatitis," *International Journal of Dermatology* 38:145-148 (1999)

Bird and Broggini, "Paroxetine Versus Amitriptyline for Treatment of Depression Associated with Rheumatoid Arthritis: A Randomized, Double Blind, Parallel Group Study," *The Journal of Rheumatology* 27:91-2797 (2000)

Bresnihan, "Treatment of Rheumatoid Arthritis with Interleukin 1 Receptor Antagonist," *Annals of Rheumatoid Disorders* 58:196-198 (1999)

Budziszewska et al., "Antidepressant Drugs Inhibit Glucocorticoid Receptor-Mediated Gene Transcription- A Possible Mechanism," *British Journal of Pharmacology* 130:1385-1393 (2000)

Calvo et al., "Pharmacokinetics of Amoxapine and its Active Metabolites," *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 23:180-185 (1985)

Carty et al., "The Biochemistry and Pharmacology of TNF $\alpha$  and  $\beta$ , 21 April 1995, New York," *Inflammation Research* 44:455-457 (1995)

Holsboer, "The Corticosteroid Receptor Hypothesis of Depression," *Neuropsychopharmacology* 23:477-501 (2000)

Jue et al., "Amoxapine: A Review of its Pharmacology and Efficacy in Depressed States," *Drugs* 24:1-23 (1982)

Kirwan, "Systemic Low-dose Glucocorticoid Treatment in Rheumatoid Arthritis," *Rheumatoid Arthritis* 27:389-403 (2001)

Koh et al., "Low Dose Amitriptyline in Ankylosing Spondylitis: A Short Term, Double Blind, Placebo Controlled Study," *The Journal of Rheumatology* 24:2158-2161 (1997)

Kristensen, "Plasma Protein Binding of Imipramine in Patients with Rheumatoid Arthritis," *European Journal of Clinical Pharmacology* 28:693-696 (1985)

Kubera et al., "Effect of Repeated Desipramine and Fluoxetine Administration on Post-Adjuvant Arthritis," *Polish Journal of Pharmacology* 52:229-235 (2000)

Lanquillon et al., "Cytokine Production and Treatment Response in Major Depressive Disorder," *Neuropsychopharmacology* 22:370-379 (2000)

Lee et al., "Effect of Steroids on the Inhibition of Platelet 5HT Uptake by Desipramine and Other Antidepressants," *European Journal of Pharmacology* 106:255-262 (1985)

Lydiard et al., "Amoxapine-- An Antidepressant with Some Neuroleptic Properties? A Review of Its Chemistry, Animal Pharmacology and Toxicology, Human Pharmacology, and Clinical Efficacy," *Pharmacotherapy* 1:163-178 (1981)

Macfarlane et al., "Trimipramine in Rheumatoid Arthritis: A Randomized Double-Blind Trial in Relieving Pain and Joint Tenderness," *Current Medical Research and Opinion* 10:89-93 (1986)

MacNeill et al., "Imipramine and Rheumatoid Factor," *Journal of International Medical Research* 4:23-27 (1976)

Maes et al., "Negative Immunoregulatory Effects of Antidepressants: Inhibition of Interferon- $\gamma$  and Stimulation of Interleukin-10 Secretion," *Neuropsychopharmacology* 20:370-379 (1999)

Maes, "Major Depression and Activation of the Inflammatory Response System," *Advances in Experimental Medicine and Biology* 461:25-46 (1999)

Maes et al., "Effects of Atypical Antipsychotics on the Inflammatory Response System in Schizophrenic Patients Resistant to Treatment with Typical Neuroleptics," *European Neuropsychopharmacology* 10:119-124 (2000)

Magni, "The Use of Antidepressants in the Treatment of Chronic Pain," *Drugs* 42:730-748 (1991)

Martelli et al., "Mechanism of Inhibition of Experimental Inflammation by Antidepressant Drugs," *European Journal of Pharmacology* 2:229-233 (1967)

Mastaglia, "Adverse Effects of Drugs on Muscle," *Drugs* 24:304-321 (1982)

McBride et al., "Management of Rheumatoid Arthritis," *Southern Medical Journal* 307-314 (1969)

McLain, "Rheumatoid Arthritis-- Update on New Therapies," *Southern Medical Journal* 94:893-895 (2001)

Michelson et al., "Imipramine Reduces the Local Inflammatory Response to Carrageenin," *Agents Actions* 42:25-28 (1994)

Morris, "Combination Drug Therapy in Rheumatoid Arthritis," *The Journal of Rheumatology* 23:1113 (1996)

Okugawa et al., "Long-Term Treatment with Antidepressants Increases Glucocorticoid Receptor Binding and Gene Expression in Cultured Rat Hippocampal Neurones," *Journal of Neuroendocrinology* 11:887-895 (1999)

Pariante et al., "Steroid-Independent Translocation of the Glucocorticoid Receptor by the Antidepressant Desipramine," *Molecular Pharmacology* 52:571-581 (1997)

Petitto et al., "Improvement of Arthritis with Fluoxetine," *Psychosomatics* 338-341

Pullar, "Combination Therapy in Rheumatoid Arthritis," *British Journal of Rheumatology* 30:311-312 (1991)

Puttini et al., "A Comparison of Dothiepin Versus Placebo in the Treatment of Pain in Rheumatoid Arthritis and the Association of Pain with Depression," *Journal of International Medical Research* 16:331-337 (1988)

Russell et al., "Combination Drug Therapy in Rheumatoid Arthritis," *The Journal of Rheumatology* 24:803-804 (1997)

Scott et al., "Use of Transdermal Amitriptyline Gel in a Patient with Chronic Pain and Depression," *Pharmacotherapy* 19:236-239 (1999)

Swinson, "Antidepressant Therapy and Rheumatoid Arthritis," *The Journal of Rheumatology* 17:277 (1990)

Tangri et al., "Anti-Inflammatory Activity of Imipramine and Congeners," *Biochemical Pharmacology* 15:825-831 (1966)

Tasset and Pesce, "Amoxapine in Human Overdose," *Journal of Analytical Toxicology*, 8:124-128 (1984)

Thorpe and Marchant-Williams, "The Role of an Antidepressant, Dibenzepin (Noveril), in the Relief of Pain in Chronic Arthritic States," *Medical Journal of Australia* 1:264-266 (1974)

Van den Berg et al., "Role of Tumour Necrosis Factor  $\alpha$  in Experimental Arthritis: Separate Activity of Interleukin 1  $\beta$  in Chronicity and Cartilage Destruction," *Annals of Rheumatoid Disorders* 58:140-148 (1999)

Vedder et al., "Regulation of Glucocorticoidreceptor-mRNA in Human Blood Cells by Amitriptyline and Dexamethasone," *Journal of Psychiatric Research* 33:303-308 (1999)

Williams, "Combination Second-Line Therapy for Rheumatoid Arthritis," *British Journal of Rheumatology* 33:603-604 (1994)

Xia et al., "Tricyclic Antidepressants Inhibit IL-6, IL-1 and TNF- $\alpha$  Release in Human Blood Monocytes and IL-2 and Interferon- $\gamma$  in T Cells," *Immunopharmacology* 34:27-37 (1996)

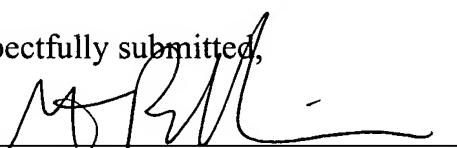
Yaron et al., "Fluoxetine and Amitriptyline Inhibit Nitric Oxide, Prostaglandin E<sub>2</sub>, and Hyaluronic Acid Production in Human Synovial Cells and Synovial Tissue Cultures," *Arthritis and Rheumatism* 42:2561-2568 (1999)

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No. 03-2095.

Date: 1/8/04

Respectfully submitted,

  
Paul T. Clark

Reg. No. 30,162

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045  
50164.006004 Information Disclosure Statement.doc



Sheet 1 of 4

SUBSTITUTE FORM PTO-1449 (MODIFIED)				U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)				Attorney Docket No.	50164/006004		
(37 C.F.R. § 1.98(b))				Serial No.	10/716,823		
				Applicant	Robyn Sackeyfo et al.		
				Filing Date	November 19, 2003		
				Group	Not yet assigned		
				IDS Filed	January 8, 2004		
				Customer No.	21559		
U.S. PATENTS							
Examiner's Initials	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date (If Appropriate)	
	4,034,087	07/05/1977	Voorhees				
	4,107,306	08/15/1978	Voorhees				
FOREIGN PATENT OR PUBLISHED FOREIGN PATENT APPLICATION							
Examiner's Initials	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation (Yes/No)	
OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)							
	Ash et al., "The Effects of Dothiepin on Subjects with Rheumatoid Arthritis and Depression," <i>Rheumatology</i> 38:959-967 (1999).						
	Barden, "Regulation of Corticosteroid Receptor Gene Expression in Depression and Antidepressant Action," <i>Journal of Psychiatry and Neuroscience</i> 24:25-39 (1999).						
	Berberian et al., "The Addition of Topical Doxepin to Corticosteroid Therapy: An Improved Treatment Regimen for Atopic Dermatitis," <i>International Journal of Dermatology</i> 38:145-148 (1999).						
	Bird and Broggini, "Paroxetine Versus Amitriptyline for Treatment of Depression Associated with Rheumatoid Arthritis: A Randomized, Double Blind, Parallel Group Study," <i>The Journal of Rheumatology</i> 27:2791-2797 (2000).						
	Bresnihan, "Treatment of Rheumatoid Arthritis with Interleukin 1 Receptor Antagonist," <i>Annals of Rheumatoid Disorders</i> 58:196-198 (1999).						
	Budziszewska et al., "Antidepressant Drugs Inhibit Glucocorticoid Receptor-Mediated Gene Transcription- A Possible Mechanism," <i>British Journal of Pharmacology</i> 130:1385-1393 (2000).						
	Calvo et al., "Pharmacokinetics of Amoxapine and its Active Metabolites," <i>International Journal of Clinical Pharmacology, Therapy, and Toxicology</i> 23:180-185 (1985).						
	Carty et al., "The Biochemistry and Pharmacology of TNF $\alpha$ and $\beta$ , 21 April 1995, New York," <i>Inflammation Research</i> 44:455-457 (1995).						
EXAMINER				DATE CONSIDERED			
EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.							



Sheet 2 of 4

SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE (MODIFIED) PATENT AND TRADEMARK OFFICE		Attorney Docket No. 50164/006004
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OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)		
Chuck et al., "The Effects of Dothiepin on Subjects with Rheumatoid Arthritis and Depression," <i>Rheumatology</i> 39:1425-1427 (2000).		
Clark, "Chronic Pain, Depression, and Antidepressants: Issues and Relationships," Johns Hopkins Arthritis Website: <a href="http://www.hopkins-arthritis.som.jhmi.edu/mngmnt/depression.html">http://www.hopkins-arthritis.som.jhmi.edu/mngmnt/depression.html</a> , October 4, 2002.		
Coupet et al., "The Effects of 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4]oxazepine (loxapine) and its Derivatives on the Dopamine-Sensitive Adenylate Cyclase of Rat Striatal Homogenates," <i>Brain Research</i> 116:177-180 (1976).		
Didonato et al., "Molecular Mechanisms of Immunosuppression and Anti-inflammatory Activities by Glucocorticoids," <i>American Journal of Respiratory and Critical Care Medicine</i> 154:S11-S15 (1996).		
Ehrenstein, "Combination Therapy in Rheumatoid Arthritis," <i>British Journal of Rheumatology</i> 34:580-581 (1995).		
Fishbain, "Evidence-based Data on Pain Relief with Antidepressants," <i>Annals of Medicine</i> 32:305-316 (2000).		
Fowler et al., "Imipramine, Rheumatoid Arthritis and Rheumatoid Factor," <i>Current Medical Research and Opinion</i> 5:241-246 (1977).		
Frank et al., "Antidepressant Analgesia in Rheumatoid Arthritis," <i>The Journal of Rheumatology</i> 15:1632-1638 (1988).		
Godefroy et al., "Do Acute or Chronic Tricyclic Antidepressants Modify Morphine Antinociception in Arthritic Rats?" <i>Pain</i> 25:233-244 (1986).		
Gupta et al., "Antidepressant Drugs in Dermatology," <i>Archives of Dermatology</i> 123:647-652 (1987).		
Gupta and Gupta, "The use of Antidepressant Drugs in Dermatology," <i>Journal of European Academy of Dermatology and Venereology</i> 15:512-518 (2001).		
Healey and Wilske, "Evaluating Combination Drug Therapy in Rheumatoid Arthritis," <i>Journal of Rheumatology</i> 18:641-642 (1991).		
Hinze-Selch et al., "Effects of Antidepressants on Weight and on the Plasma Levels of Leptin, TNF- $\alpha$ and Soluble TNF Receptors: A Longitudinal Study in Patients Treated with Amitriptyline or Paroxetine," <i>Neuropsychopharmacology</i> 23:13-19 (2000).		
Holsboer, "The Corticosteroid Receptor Hypothesis of Depression," <i>Neuropsychopharmacology</i> 23:477-501 (2000).		
Jue et al., "Amoxapine: A Review of its Pharmacology and Efficacy in Depressed States," <i>Drugs</i> 24:1-23 (1982).		
Kirwan, "Systemic Low-dose Glucocorticoid Treatment in Rheumatoid Arthritis," <i>Rheumatoid Arthritis</i> 27:389-403 (2001).		
Koh et al., "Low Dose Amitriptyline in Ankylosing Spondylitis: A Short Term, Double Blind, Placebo Controlled Study," <i>The Journal of Rheumatology</i> 24:2158-2161 (1997).		
Kristensen, "Plasma Protein Binding of Imipramine in Patients with Rheumatoid Arthritis," <i>European Journal of Clinical Pharmacology</i> 28:693-696 (1985).		
Kubera et al., "Effect of Repeated Desipramine and Fluoxetine Administration on Post-Adjuvant Arthritis," <i>Polish Journal of Pharmacology</i> 52:229-235 (2000).		
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Lanquillon et al., "Cytokine Production and Treatment Response in Major Depressive Disorder," <i>Neuropsychopharmacology</i> 22:370-379 (2000).		
Lee et al., "Effect of Steroids on the Inhibition of Platelet 5HT Uptake by Desipramine and Other Antidepressants," <i>European Journal of Pharmacology</i> 106:255-262 (1985).		
Lydiard et al., "Amoxapine-- An Antidepressant with Some Neuroleptic Properties? A Review of Its Chemistry, Animal Pharmacology and Toxicology, Human Pharmacology, and Clinical Efficacy," <i>Pharmacotherapy</i> 1:163-178 (1981).		
Macfarlane et al., "Trimipramine in Rheumatoid Arthritis: A Randomized Double-Blind Trial in Relieving Pain and Joint Tenderness," <i>Current Medical Research and Opinion</i> 10:89-93 (1986).		
MacNeill et al., "Imipramine and Rheumatoid Factor," <i>Journal of International Medical Research</i> 4:23-27 (1976).		
Maes et al., "Negative Immunoregulatory Effects of Antidepressants: Inhibition of Interferon- $\gamma$ and Stimulation of Interleukin-10 Secretion," <i>Neuropsychopharmacology</i> 20:370-379 (1999).		
Maes, "Major Depression and Activation of the Inflammatory Response System," <i>Advances in Experimental Medicine and Biology</i> 461:25-46 (1999).		
Maes et al., "Effects of Atypical Antipsychotics on the Inflammatory Response System in Schizophrenic Patients Resistant to Treatment with Typical Neuroleptics," <i>European Neuropsychopharmacology</i> 10:119-124 (2000).		
Magni, "The Use of Antidepressants in the Treatment of Chronic Pain," <i>Drugs</i> 42:730-748 (1991).		
Martelli et al., "Mechanism of Inhibition of Experimental Inflammation by Antidepressant Drugs," <i>European Journal of Pharmacology</i> 2:229-233 (1967).		
Mastaglia, "Adverse Effects of Drugs on Muscle," <i>Drugs</i> 24:304-321 (1982).		
McBride et al., "Management of Rheumatoid Arthritis," <i>Southern Medical Journal</i> 307-314 (1969).		
McLain, "Rheumatoid Arthritis-- Update on New Therapies," <i>Southern Medical Journal</i> 94:893-895 (2001).		
Michelson et al., "Imipramine Reduces the Local Inflammatory Response to Carrageenin," <i>Agents Actions</i> 42:25-28 (1994).		
Morris, "Combination Drug Therapy in Rheumatoid Arthritis," <i>The Journal of Rheumatology</i> 23:1113 (1996).		
Okugawa et al., "Long-Term Treatment with Antidepressants Increases Glucocorticoid Receptor Binding and Gene Expression in Cultured Rat Hippocampal Neurones," <i>Journal of Neuroendocrinology</i> 11:887-895 (1999).		
Pariante et al., "Steroid-Independent Translocation of the Glucocorticoid Receptor by the Antidepressant Desipramine," <i>Molecular Pharmacology</i> 52:571-581 (1997).		
Petitto et al., "Improvement of Arthritis with Fluoxetine," <i>Psychosomatics</i> 338-341.		
Pullar, "Combination Therapy in Rheumatoid Arthritis," <i>British Journal of Rheumatology</i> 30:311-312 (1991).		
Puttini et al., "A Comparison of Dothiepin Versus Placebo in the Treatment of Pain in Rheumatoid Arthritis and the Association of Pain with Depression," <i>Journal of International Medical Research</i> 16:331-337 (1988).		
Russell et al., "Combination Drug Therapy in Rheumatoid Arthritis," <i>The Journal of Rheumatology</i> 24:803-804 (1997).		
Scott et al., "Use of Transdermal Amitriptyline Gel in a Patient with Chronic Pain and Depression," <i>Pharmacotherapy</i> 19:236-239 (1999).		
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Tangri et al., "Anti-Inflammatory Activity of Imipramine and Congeners," <i>Biochemical Pharmacology</i> 15:825-831 (1966).				
Tasset and Pesce, "Amoxapine in Human Overdose," <i>Journal of Analytical Toxicology</i> , 8:124-128 (1984).				
Thorpe and Merchant-Williams, "The Role of an Antidepressant, Dibenzepin (Noveril), in the Relief of Pain in Chronic Arthritic States," <i>Medical Journal of Australia</i> 1:264-266 (1974).				
Van den Berg et al., "Role of Tumour Necrosis Factor $\alpha$ in Experimental Arthritis: Separate Activity of Interleukin 1 $\beta$ in Chronicity and Cartilage Destruction," <i>Annals of Rheumatoid Disorders</i> 58:140-148 (1999).				
Vedder et al., "Regulation of Glucocorticoidreceptor-mRNA in Human Blood Cells by Amitriptyline and Dexamethasone," <i>Journal of Psychiatric Research</i> 33:303-308 (1999).				
Williams, "Combination Second-Line Therapy for Rheumatoid Arthritis," <i>British Journal of Rheumatology</i> 33:603-604 (1994).				
Xia et al., "Tricyclic Antidepressants Inhibit IL-6, IL-1 and TNF- $\alpha$ Release in Human Blood Monocytes and IL-2 and Interferon- $\gamma$ in T Cells," <i>Immunopharmacology</i> 34:27-37 (1996).				
Yaron et al., "Fluoxetine and Amitriptyline Inhibit Nitric Oxide, Prostaglandin E <sub>2</sub> , and Hyaluronic Acid Production in Human Synovial Cells and Synovial Tissue Cultures," <i>Arthritis and Rheumatism</i> 42:2561-2568 (1999).				
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